Circulating Tumor Cells (CTCs) in patients with extensive stage small cell lung cancer and their association with clinical outcome

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Background: The NOTCH pathway has been identified as a key therapeutic pathway in SCLC. Tarextumab (TRXT, anti-Notch2/3, OMP-99R56) is a fully human monoclonal antibody that targets the Notch2 and Notch3 receptors. PINNACLE is a Phase 1b trial of TRXT in combination with etoposide and platinum therapy (EP) in patients with untreated extensive stage small cell lung cancer (ES-SCLC). Baseline CTCs and post treatment changes in CTCs have previously been shown to predict the response to chemotherapy in SCLC. CTCs may also serve as pharmacodynamic (PD) biomarkers. Here we describe a study of baseline and longitudinal CTCs in ES-SCLC patients from the PINNACLE phase 1b trial (clinicaltrials.gov: NCT01869741).

Materials and methods: CTCs, CTC clusters, apoptotic CTCs and N-cadherin+CTCs were identified and enumerated from patient blood samples using Epic Sciences CTC technology. Baseline CTCs from 26 patients were correlated with clinical outcome. Progression free survival (PFS), overall survival (OS) and best overall response (BOR). Multivariate analysis was performed to identify CTC numbers in a subset of time points to correlate with response to treatment. Results: CTCs were present in 81% of the patients (21/26). CTC clusters and apoptotic CTCs were detected in 38% and 77% of the patients, respectively. At baseline, CTC counts 5/mL were significantly associated with poor OS (p=0.04). There was a trend that the presence of CTC clusters was associated with worse OS. With a cut-off of 3.4/mL, apoptotic CTCs showed a trend in association with overall survival. CTC numbers in patients with liver metastasis were significantly higher than in patients without liver metastasis. CTCs were also found to be correlated significantly with the number of metastatic sites. When measured at Day 7 post dosing, CTC numbers were significantly decreased. Conclusions: Our findings suggest that CTCs are frequently detectable in patients and are a prognostic factor in ES-SCLC. CTC decreases with TRXT and platinum-based chemotherapy. Updated results will be presented. CTCs will be further evaluated in the Phase 2 portion of the PINNACLE trial.

Abstract

Potential PD Effect at 7 Days Post Dosing

Cycle 1 Day 8: Best Predictor of Outcome

Baseline CTCs are Associated with Survival and Metastasis

Baseline CTC counts were significantly associated with overall survival (CTC/mL=5: n=10; CTC/mL=15: n=6; n=16). CTC clusters and apoptotic CTC counts showed a trend in association with overall survival (CTC cluster=0: n=16; CTC cluster=1: n=10; Apoptotic CTCs=0: n=11; Apoptotic CTCs>3.4: n=5; 11). Baseline CTC counts were also associated with number of metastatic sites and liver metastasis.

Potential effects model: 0.0162).

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